

Platelet response to clopidogrel: the paradox of obesity or leanness?

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Obesity is a growing health problem associated with numerous other pathologies, primarily with cardiovascular (CV) diseases and diabetes. Moreover, adipose tissue is at present considered to be an important endocrine organ, which produces adipose-derived hormones—adipokines.^{1,2} The so called “obesity paradox” described in patients with cardiovascular diseases³ confirms a complex role of adipose tissue and its properties to modulate numerous physiological and pathological processes.

Dual antiplatelet therapy (DAPT) is a gold standard of treatment after percutaneous coronary intervention (PCI) with stent implantation, and its efficacy is indispensable for the success of the procedure and improvement in patient survival. Despite a well-grounded position of antiplatelet drugs in CV pharmacotherapy, low response to those drugs is relatively common.⁴ There have been attempts to overcome the resistance of platelets to clopidogrel, for example, by increasing its dose⁵ or adding omega-3 polyunsaturated fatty acids.⁶ Moreover, there are new promising antiplatelet drugs administered in patients with acute coronary disease, such as prasugrel, ticagrelor, and cangrelor. They have been shown to be more potent antiplatelet strategies, simultaneously raising concerns on a possible increase of bleeding risk compared with clopidogrel. Further studies with new antiplatelet drugs are required to assess their efficacy and safety in patients with stable coronary artery disease (CAD), especially in those with low platelet response to clopidogrel. Considering the extent of the problem and fundamental role of antiplatelet drugs, it is important to identify factors that may affect platelet reactivity. Obesity is considered one of them.⁸ However, it is possible that high on-treatment platelet reactivity (HTPR) is not associated with obesity per se, but with other risk factors that are found more commonly in untreated obese patients.

Impaired platelet response to a loading dose of clopidogrel in obese patients, and similar platelet

reactivity during chronic DAPT with clopidogrel and acetylsalicylic acid among obese and normal-weight individuals are the main findings of the article by Haberka et al,⁹ published in the current issue of the *Polish Archives of Internal Medicine*. One of strong points of the study was a homogenous study group, which consisted solely of patients with stable CAD after elective PCI with stent implantation. Moreover, unlike most of other studies, Haberka et al⁹ assessed platelet function not only early after the administration of a loading dose of clopidogrel, but also 1 month after PCI during DAPT. It may shed additional light on the problem, since the majority of previous studies have assessed only early platelet reactivity and extrapolated the results to an overall on-treatment platelet response.

The authors claimed that the association between obesity and platelet reactivity was complex and biphasic. Noteworthy, platelet response to clopidogrel deteriorated in all 3 groups: lean, overweight, and obese. In obese patients, platelet reactivity when stimulated with ADP (which is a measure of their response to clopidogrel) was higher after the loading dose of clopidogrel and increased slightly 1 month after PCI. Of note, in the lean group, it increased twice over 1 month. However, it is unclear whether those changes in time were significant. Nonetheless, similar platelet reactivity after 1 month of a maintenance dose of clopidogrel in obese, overweight, and lean patients was mainly the result of deterioration in platelet response to clopidogrel in lean patients. Interestingly, the change in platelet reactivity was inversely associated with body mass index and waist circumference. In other words, the thinner the person was, the higher the increase in platelet reactivity developed over time. According to Haberka et al,⁹ one may observe the “leanness paradox” in a deteriorating platelet response to clopidogrel. A multivariate analysis showed that besides BMI, also creatinine, male sex, and active smoking were the independent predictors of the worsening of platelet response to clopidogrel.

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It has been shown that low platelet response to clopidogrel is more common in patients with cytochrome P450 2C19 loss-of-function polymorphism, and, interestingly, it increases overtime in this group.⁶ Therefore, it would have been reasonable to perform genetic testing for that polymorphism, since it is a factor that may affect platelet function. It is possible that in a relatively small population of the study by Haberka et al.,⁹ the proportion of those with cytochrome P450 2C19 loss-of-function polymorphism was higher in the lean group, which might have distorted the results. As far as we are considered, the article is the first to demonstrate an increase in platelet reactivity on chronic DAPT in lean patients. It may well be that the lean population in the study was a combination of fit individuals and those with unintentional weight loss due to underlying conditions such as frailty or other undiagnosed chronic diseases. The inflammatory reaction related to those disorders might have affected platelet function.

The relationship between platelet reactivity and inflammation was also assessed by Haberka et al.⁹ Authors assayed the easily obtainable and non-specific markers of the inflammatory state, such as white blood count, neutrophil and lymphocyte counts, and neutrophil-to-lymphocyte ratio. They found that baseline WBC was predictive of platelet response to a loading dose of clopidogrel and was not associated with platelet reactivity on chronic clopidogrel treatment. On the other hand, baseline lymphocyte count was associated with platelet function both at baseline and during follow-up. Nonetheless, inflammatory markers were assayed only at baseline, which is a shortcoming of the study.

PCI-induced injury of the endothelium is a strong proinflammatory stimulus. We found that systemic inflammatory reaction triggered by PCI with stent implantation persists at least 1 month after the procedure, and may also account for lower platelet response to clopidogrel.¹⁰ On the other hand, systemic low-grade inflammation related to fat tissue, which contributes to increased platelet turnover in obese individuals, may also alter the effect of antiplatelet drugs. Thus, some authors suggested a dose adjustment of clopidogrel in obese patients,¹¹ despite the fact that there is no evidence from clinical trials on the benefit of this approach.¹² Additionally, it has been shown previously that inflammatory response triggered by PCI may modulate endocrine activity of the adipose tissue and result in a decrease of adiponectin and increase of leptin concentrations early after the procedure.¹³ Therefore, it is possible that changes of adipokines' pattern during follow-up after PCI may account, at least in part, for platelet response to clopidogrel and the differences between lean and obese individuals. It would be interesting to assess platelet reactivity along with fat tissue endocrine function and inflammatory indicators in a long-term follow-up after PCI with stent implantation in terms of the explanation of the "obesity paradox".

The shortcoming of the study by Haberka et al.⁹ is a limited study group, especially small number of lean patients (26 of 130 patients), which may have distorted the results. Moreover, it would be interesting to present the subgroup characteristics (eg, sex, smoking, creatinine levels, and the presence of various comorbidities) that might have affected platelet reactivity. It seems to be particularly important because those factors have been found to be independent predictors of the change in platelet response to clopidogrel in the multivariate analysis. Similarly, there is no information about differences in inflammatory markers between the subgroups, even though leukocytes have been associated with platelet reactivity.

In summary, despite the fact that obesity is generally perceived as a risk factor of high on-treatment platelet reactivity on chronic clopidogrel therapy, the data provided by Haberka et al.⁹ suggest the "leanness paradox", that is, a surprising increase in platelet reactivity in lean patients 1 month after PCI. It may be particularly dangerous because platelet reactivity is usually assayed once, just after PCI. Therefore, although it is not recommended by the current guidelines, monitoring of platelet reactivity on DAPT, especially in lean patients, may be advisable in order to diagnose those with deteriorating clopidogrel response. Moreover, it may help identify and verify the risk factors for HTPR. Finally, further research on a larger population is needed to test the hypothesis of the "leanness paradox."

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